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EDITORIAL

# Serial lactate measurements to guide resuscitation: more evidence not to?

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Serum lactate has long been considered a biomarker of tissue perfusion and a trigger for fluid administration in critically ill patients, especially in those with sepsis [1]. The Sepsis-3 consensus defined septic shock based on vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and a serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia incorporated plasma lactate in the criteria for septic shock [2]. The choice to include serum lactate was based on prognostic stratification, with patients with hypotension requiring vasopressors and elevated serum lactate levels with higher mortality than patients meeting only one criterion (i.e., isolated elevated lactate or hypotension requiring vasopressors without elevated lactate). Finally, the panel acknowledged that serum lactate measurements are relatively commonly available [2]. The 2021 edition of the Surviving Sepsis Campaign (SCCM) suggests guiding resuscitation to decrease serum lactate levels in patients with elevated lactate levels. Despite the widespread use of lactate to guide fluid resuscitation, evidence to support this practice is very limited, and the panel issued a weak recommendation [3].

In a randomized trial which enrolled patients with sepsis with serum lactate levels greater than or equal to 3.0 mEq/L from Dutch mixed intensive care units (ICUs) [3], a strategy guided by lactate levels to decrease lactate by 20% or more per 2 h for the initial 8 h of ICU stay was associated with lower in-hospital mortality than no knowledge of lactate levels (except for the admission value) (43.5% (77/177) vs. 33.9% (58/171), respectively ($p=0.067$), adjusted hazard ratio, 0.61; 95% confidence interval 0.43–0.87; $p=0.006$). The difference in fluid administered during the first 8 h was minimal between the two groups (2194 ± 1669 mL vs. 2697 ± 1965 mL, $p=0.01$) and very unlikely to explain the difference in outcome. Of note, significantly more patients in the "lactate group" received vasodilators than in the control group (43% vs. 20%, $p<0.001$). In another multi-center trial among patients with sepsis in the United States [4], patients were randomized to a strategy based on lactate clearance or to normalize central venous oxygenation ($ScvO_2$) to >70%. The in-hospital mortality rates were 23% in the $ScvO_2$ group and 25% in the lactate clearance group, respectively. No differences in fluid administration were observed between the two groups.

More recently, the ANDROMEDA-SHOCK study [5] enrolled patients with septic shock across 28 intensive care units in 5 countries to guide initial resuscitation based on peripheral perfusion assessment or lactate clearance. The mortality on day 28 was 34.9% in the peripheral perfusion group and 43.4% in the lactate group (hazard ratio, 0.75 [95% CI 0.55 to 1.02]; $p=0.06$). Patients in the peripheral perfusion group received less resuscitation fluid within the first 8 h (mean difference, −408 mL [95% CI −705 to −110]; $p=0.01$). A Bayesian reanalysis suggested [6] lower mortality in the peripheral perfusion group.

Overall, the results of previous randomized trials do not suggest that a lactate-guided strategy improves survival. Altogether, these results raise the question of the relevance of guiding resuscitation, including fluid administration, on repeated lactate measurements.

Serum lactate level is poorly specific for hypoperfusion [7]. The basal lactate production is about 0.8 mmol $kg^{-1}$ $h^{-1}$ (more than 1300 mmol $day^{-1}$ in a 70 kg patient). Increased lactate production can arise from increased anaerobic glycolysis and aerobic glycolysis production

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(e.g., increased pyruvate production after $\beta_2$ receptor activation or intense stress). In a post hoc analysis of the multi-center ALBIOS (Albumin Italian Outcome Sepsis) trial [8], which investigated the impact of albumin on outcome in patients with sepsis, elevated serum lactate was more often associated with impaired tissue oxygen use rather than decreased perfusion. Other factors affect serum lactate levels, including impaired mitochondrial function or reduced hepatic clearance (the liver accounts for approximately 70% of lactate metabolism, Fig. 1).

In this issue of the journal, Ahlstedt et al. [9] provided another piece to the puzzle of time-to-resolution of hyperlactatemia in septic shock according to the fluid strategy used. They conducted a post hoc analysis of serial plasma lactate concentrations in a sub-cohort of 777 patients from the international multi-center clinical CLASSIC trial (Restriction of intravenous fluids in ICU Patients with Septic Shock) [10]. In the CLASSIC trial [11], the restrictive group could receive fluid boluses only in case of severe hypotension or hypoperfusion, while fluid administration in the standard group was mostly based on the SCCM guidelines. Between day 1 and 3, patients received a median of 5334 (3476–7578) ml vs. 6919 (4721–9744) ml of fluids in the restrictive and liberal group, respectively. The authors observed that a restrictive intravenous fluid therapy strategy did not affect the time-to-resolution of hyperlactatemia compared to standard fluid therapy (hazard ratios for resolution of hyperlactatemia of 1.21 (0.89–1.65) on day 2–3 in the restrictive vs. standard group, respectively). These results were consistent among patients with higher baseline lactate levels. The findings of this study suggest that there is no impact of a liberal fluid strategy vs. a more restrictive strategy on both lactate clearance and outcome. Of note, this was a post hoc analysis of a multi-center trial, which enrolled a fraction of the population of 1,554 patients enrolled in the original CLASSIC trial; therefore, the results should be considered exploratory. Furthermore, the protocol considered fluid boluses for patients with serum lactate levels > 4 mmol/L in the restrictive group, confounding the association between the fluid strategy and outcome.

Altogether, the current literature on sepsis does not support lactate as an accurate biomarker of hypoperfusion, or that guiding treatment based on serial measurements would improve outcomes. Potential harm may result from serial measurements with excessive fluids or excess of vasopressors. However, lactate measurement remains an easy-to-measure biomarker with a prognostic value. Better integration of serum lactate with clinical phenotyping [12] and the use of peripheral perfusion assessment could provide better individualized strategies [5]. Ongoing clinical trials will provide insights into the optimal approach to guide fluid therapy for sepsis [13–15], but lactate clearance as the target is further weakened.

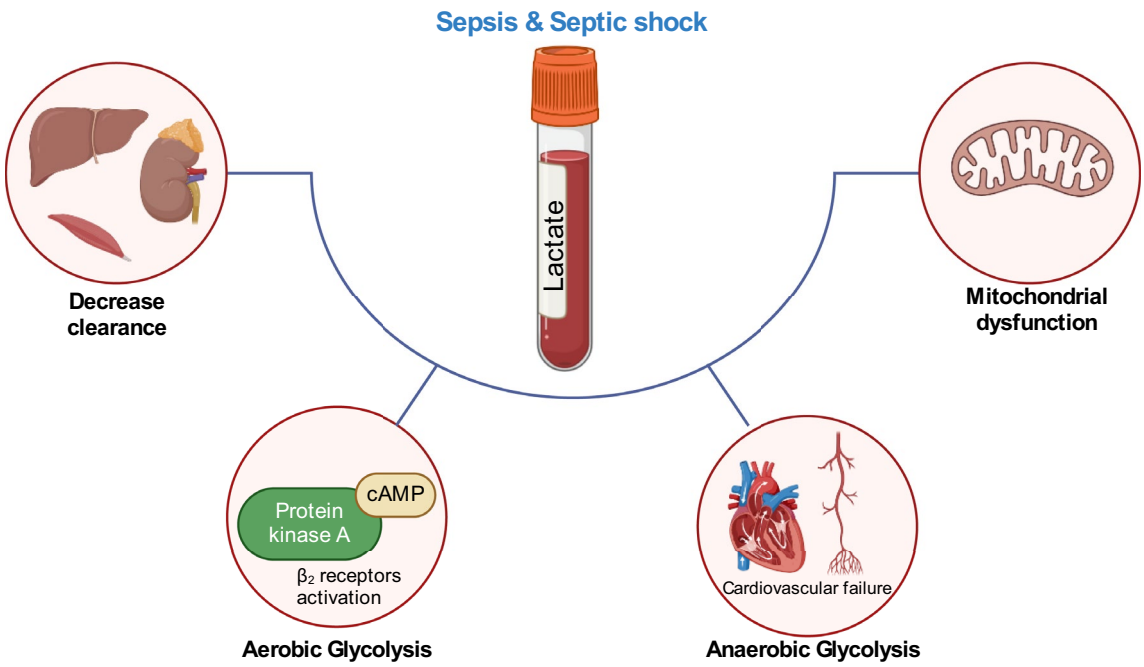


**Fig. 1** Mechanisms impacting serum lactate level in sepsis and septic shock

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**Author contributions**
All authors wrote and approved the editorial.

**Declarations**

**Conflicts of interest**
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